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# Hyperlactatemia is an independent predictor of mortality and denotes distinct subtypes of severe sepsis and septic shock☆,☆☆

Daniel O. Thomas-Rueddel, MD [a,b,*], Bernhard Poidinger, MD [a], Manfred Weiss, MD [c], Friedhelm Bach, MD [d], Karin Dey, MD [e], Helene Häberle, MD [f], Udo Kaisers, MD [g], Hendrik Rüddel, MD [a,b], Dirk Schädler, MD [h], Christian Scheer, MD [i], Torsten Schreiber, MD [j], Tobias Schürholz, MD [k], Philipp Simon, MD [g], Armin Sommerer, MD [e], Daniel Schwarzkopf, MSc [b], Andreas Weyland, MD [l], Gabriele Wöbker, MD [m], Konrad Reinhart, MD [a,b], Frank Bloos, MD, PhD [a,b] for the Medical Education for Sepsis Source Control and Antibiotics study group

[a] Department of Anesthesiology and Intensive Care Medicine, Jena University Hospital, Jena, Germany
[b] The Integrated Research and Treatment Center for Sepsis Control and Care, Jena University Hospital, Jena, Germany
[c] Department of Anesthesiology, University Hospital Ulm, Ulm, Germany
[d] Department of Anesthesiology, Intensive Care Medicine, Emergency Medicine and Pain Therapy, Ev. Krankenhaus Bielefeld, Bielefeld, Germany
[e] Department of Anesthesiology and Intensive Care Medicine, Bundeswehrkrankenhaus Berlin, Berlin, Germany
[f] Department of Anesthesiology and Intensive Care Medicine, University Hospital Tübingen, Tübingen, Germany
[g] Department of Anesthesiology and Intensive Care Medicine, University Hospital Leipzig, Leipzig, Germany
[h] Department of Anesthesiology and Intensive Care Medicine, University Medical Center Schleswig-Holstein, Campus Kiel, Germany
[i] Department of Anesthesiology and Intensive Care Medicine, Ernst-Moritz-Arndt-University Greifswald, Greifswald, Germany
[j] Department of Anesthesiology and Intensive Care Medicine, Zentralklinik Bad Berka GmbH, Bad Berka, Germany
[k] Department of Intensive Care Medicine, University Hospital Aachen, Aachen, Germany
[l] Department of Anesthesiology, Intensive Care Medicine, Emergency Medicine, and Pain Therapy, Hospital Oldenburg, Oldenburg, Germany
[m] Department of Intensive Care Medicine, HELIOS Klinikum Wuppertal, Wuppertal, Germany

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ABSTRACT

*Purpose:* Current guidelines and most trials do not consider elevated lactate (Lac) serum concentrations when grading sepsis severity. We therefore assessed the association of different types of circulatory dysfunction regarding presence of hyperlactatemia and need for vasopressor support with clinical presentation and outcome of sepsis.
*Methods:* In a secondary analysis of a prospective observational multicenter cohort study, 988 patients with severe sepsis were investigated regarding vasopressor support, Lac levels, and outcome.
*Results:* Twenty-eight–day mortality regarding shock or hyperlactatemia was as follows: hyperlactatemia more than 2.5 mmol/L and septic shock (tissue dysoxic shock): 451 patients with a mortality of 44.8%; hyperlactatemia without vasopressor need (cryptic shock): 72 patients, mortality 35.3%; no hyperlactatemia with vasopressor need (vasoplegic shock): 331 patients, mortality 27.7%; and absence of hyperlactemia or overt shock (severe sepsis): 134 patients, mortality 14.2% ($P < .001$). These groups showed differences in source and origin of infection. The influence of hyperlactatemia on 28-day mortality ($P < .001$) (odds ratio 3.0, 95% confidence interval 2.1-4.1 for Lac >4 mmol/L) was independent of vasopressor support ($P < .001$) (odds ratio 2.0, 95% confidence interval 1.3-3.0 for norepinephrine >0.1 μg/kg per minute) in logistic regression.
*Conclusions:* Hyperlactatemia increases risk of death independent of vasopressor need resulting in different phenotypes within the classic categories of severe sepsis and septic shock.


## 1. Introduction

Sepsis is frequently complicated by the development of multiorgan dysfunction syndrome. Tissue perfusion is severely compromised in sepsis, which significantly contributes to the development organ dysfunction [1]. However, the clinical identification of hypoperfusion in sepsis, severe sepsis, and septic shock varied significantly during the last 2 decades. The first widely accepted definitions were published after a consensus conference in 1992 [2], which were conceived to

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* Corresponding author at: Center for Sepsis Control and Care, Department of Anesthesiology and Intensive Care Medicine, Jena University Hospital, Erlanger Allee 101, 07740 Jena, Germany. Tel.: +49 3641 9323267, +49 177 3134248 (mobile); fax: +49 3641 9323102.
*E-mail address:* daniel.thomas@med.uni-jena.de (D.O. Thomas-Rueddel).

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identify clinically recognizable stages along a continuum of disease severity. *Septic shock* was defined as sepsis-induced hypotension along with the presence of perfusion abnormalities. The latter included lactic acidosis, oliguria, or altered mental status [2]. In 2001, the International Sepsis Definitions Conference omitted the signs of hypoperfusion from the definition of septic shock for adult patients [3]. Many septic shock trials used adapted versions of the 2001 definitions, where *septic shock* was defined as arterial hypotension or vasopressor need [4-7]. Some trials used modified versions of the 1992 definitions [8,9]. The 2012 Surviving Sepsis Campaign guidelines hold on to the 2001 definition of septic shock amended by 2 different definitions of tissue hypoperfusion. One definition consists of arterial hypotension, hyperlactatemia more than 1 mmol/L, or oliguria. The second definition includes arterial hypotension or blood lactate (Lac) concentrations of at least 4 mmol/L.

Different entities within the spectrum of sepsis-induced circulatory dysfunction have been described in recent publications [10]. These include cryptic shock [11-13] and occult hypoperfusion [14] (hyperlactatemia without hypotension), overt shock [12,15,16] (sustained hypotension or need for vasopressor support), nonsustained hypotension [16] (short episodes of hypotension), vasoplegic shock [13,15] (sustained hypotension or need for vasopressor support without hyperlactatemia), and (tissue) dysoxic shock [13,15] (sustained hypotension or need for vasopressor support accompanied by hyperlactatemia). None has gained universal acceptance, and there is no consensus about the exact definitions of these terms.

An association of mortality and elevated Lac levels has been demonstrated in unselected hospitalized patients with infections [17]. This association was independent of hypotension in patients with infections in the emergency department [14,18]. Presence of hyperlactatemia was associated with a significantly increased mortality in patients with vasopressor-dependent septic shock [10,13,15,19,20]. Potentially, this hyperlactatemia represents a persistent perfusion deficit. However, 2 groups reported very low mortality rates below 10% in septic shock patients with Lac values below 2.5 mmol/L [10,20] or 2 mmol/L [15]. These data suggest that presence of hyperlactatemia would add significant information to the severity classification of sepsis.

The aim of the present investigation was to analyze the distribution and characteristics of different types of sepsis-induced circulatory dysfunction defined by the presence of hyperlactatemia and the need for vasopressor support in a large patient population. A secondary study goal was to assess the impact of elevated Lac levels on outcome beyond the commonly used classification of sepsis severity, that is, severe sepsis and septic shock.

## 2. Methods

### 2.1. Study design

This is a secondary analysis of a longitudinal multicenter observational cohort study in 44 German hospitals. The methods of the original study have been described previously [21]. Briefly, patients with new onset of severe sepsis treated in an intensive care unit (ICU) were documented in an observatory design. The study had a pragmatic design with a short case report form to allow participation of hospitals without research staff and served as a run-in study for a cluster-randomized trial assessing the question whether a multifaceted educational program accelerates the onset of antibiotic therapy and improves survival (Medical Education for Sepsis Source Control and Antibiotics, ClinicalTrials.gov identifier NCT01187134).

### 2.2. Patients

Between December 2010 and April 2011, all consecutive adult patients treated in the participating ICUs for proven or suspected infection with at least 1 new organ dysfunction related to the infection were eligible for inclusion. Patients were excluded who received initial infection control measures for sepsis in another hospital, who did not receive full life-sustaining treatment at the time of sepsis onset, or who were never treated in an ICU. The study was reviewed and approved by the local ethics' committees, which waived the need for informed consent due to the observational character of the study. Responsible data protection officials also approved the study.

### 2.3. Data collection

Documentation included patient demographics, origin and onset of infection, ICU, hospital, and 28-day mortality. Highest values but not parameter changes of serum Lac, procalcitonin (PCT), and basic laboratory values as well as vital signs were recorded within the first 24 hours after the onset of severe sepsis. Severity of disease was assessed by the Simplified Acute Physiology Score II and severity of organ dysfunctions by the Sequential Organ Failure Assessment (SOFA) score, including subscores, within 24 hours after the onset of severe sepsis. Data were collected in a Web-based electronic case report form (OpenClinica, Waltham, MA). Data integrity was confirmed by data checks within the database resulting in queries to the investigators where applicable.

### 2.4. Data analysis

Lactate values were stratified into 3 categories. According to previous publications, cutoff values of 2.5 mmol/L [10,14,20] and 4 mmol/L [13,14,17,18,22], respectively, were chosen. Hyperlactatemia was defined as serum Lac concentration of at least 2.5 mmol/L. Overt shock [12,15] was defined as any vasopressor support according to SOFA subscores and further stratified into low-dose ($\leq$0.1 $\mu$g/kg per minute norepinephrine) and high-dose (>0.1 $\mu$g/kg per minute norepinephrine) vasopressor support. For further analysis, we divided patients into 4 groups according to the presence of hyperlactatemia and vasopressor support: (i) severe sepsis without shock: absence of vasopressor support or hyperlactatemia, (ii) cryptic shock: hyperlactatemia in the absence of vasopressor support [11-13], (iii) vasoplegic shock: vasopressor support in the absence of hyperlactatemia [13,15], and (iv) tissue dysoxic shock, defined by the combination of vasopressor support and hyperlactatemia [13,15] (Fig. 1).

Differences were tested by $\chi^2$ test or Kruskal-Wallis test as appropriate with Z test and multiple comparison test according to Kruskal-Wallis for post hoc comparisons. Survival curves to hospital discharge were compared by pairwise log-rank test. A logistic regression model was used to assess the influences of vasopressor and Lac categories on 28-day mortality corrected for age. To further analyze the association of increasing Lac levels and 28-day mortality, local polynomial regression fitting (LOESS) [23] was performed. An $\alpha$ of .05 was considered as significant, confidence intervals are given at the 95% level. Categorical data are expressed as absolute and relative frequencies, and continuous data are expressed as median and interquartile range. Analyses were performed using IBM SPSS Statistics 19.0 (SPSS Inc, Chicago, IL), multiple comparison test according to Kruskal-Wallis and LOESS was performed by R version 3.0.3 (R Development Core Team 2013).

## 3. Results

### 3.1. Patients, Lac, and vasopressor support

In total, 1042 patients were included in the longitudinal multicenter observational cohort study during the 5 months study period. Of these, 54 patients were excluded due to missing values in Lac or cardiovascular SOFA subscore resulting in 988 evaluable patients.

Distribution into predefined categories is shown in Fig. 1. Patient demographics, initial clinical characteristics, and outcome parameters are shown in Table 1. Serum Lac levels were below 2.5 mmol/L in 465 patients (47.1%), between 2.5 and 4 mmol/L in 202 (20.4%) patients, and higher than 4 mmol/L in 321 (32.5%) patients.

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